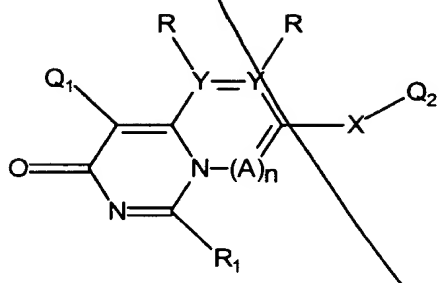
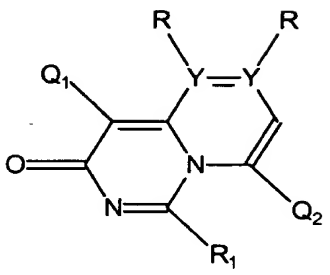
CLAIMS

We claim:

1. A compound of the formula:



(Ia) or



(Ib),

wherein:

each of Q_1 and Q_2 are independently selected from 5-6 membered aromatic carbocyclic or heterocyclic ring systems, or 8-10 membered bicyclic ring systems consisting of aromatic carbocyclic rings, aromatic heterocyclic rings or a combination of an aromatic carbocyclic ring and an aromatic heterocyclic ring; wherein:

Q_1 is substituted with 1 to 4 substituents, independently selected from halo; C_1-C_3 alkyl optionally substituted with NR'_2, OR', CO_2R' or $CONR'_2$; O-(C_1-C_3)-alkyl optionally substituted with NR'_2, OR', CO_2R' or $CONR'_2$; NR'_2; OCF_3; CF_3; NO_2; CO_2R'; $CONR'$; SR'; $S(O_2)N(R')_2$; SCF_3; CN; $N(R')C(O)R^4$; $N(R')C(O)OR^4$; $N(R')C(O)C(O)R^4$; $N(R')S(O_2)R^4$; $N(R')R^4$; $N(R^4)_2$; OR^4; $OC(O)R^4$; $OP(O)_3H_2$; or $N=C-N(R')_2$; and

Q_2 is optionally substituted with up to 4 substituents, independently selected from halo; C_1-C_3 straight or branched alkyl optionally substituted with

NR'_2, OR', CO_2R', $S(O_2)N(R')_2$, N=C-$N(R')_2$, R^3, or $CONR'_2$; O-(C_1-C_3)-alkyl optionally substituted with NR'_2, OR', CO_2R', $S(O_2)N(R')_2$, N=C-$N(R')_2$, R^3, or $CONR'_2$; NR'_2; OCF_3; CF_3; NO_2; CO_2R'; CONR'; R^3; OR^3; NR^3; SR^3; $C(O)R^3$; $C(O)N(R')R^3$; $C(O)OR^3$; SR'; $S(O_2)N(R')_2$; SCF_3; N=C-$N(R')_2$; or CN;

wherein R' is selected from hydrogen, (C_1-C_3)-alkyl; (C_2-C_3)-alkenyl or alkynyl; phenyl or phenyl substituted with 1 to 3 substituents independently selected from halo, methoxy, cyano, nitro, amino, hydroxy, methyl or ethyl;

R^3 is selected from a 5-6 membered aromatic carbocyclic or heterocyclic ring system; and

R^4 is (C_1-C_4)-alkyl optionally substituted with $N(R')_2$, OR', CO_2R', $CON(R')_2$, or $SO_2N(R^2)_2$; or a 5-6 membered carbocyclic or heterocyclic ring system optionally substituted with $N(R')_2$, OR', CO_2R', $CON(R')_2$, or $SO_2N(R^2)_2$;

X is selected from -S-, -O-, $-S(O_2)-$, -S(O)-, $-S(O_2)-N(R^2)-$, $-N(R^2)-S(O_2)-$, $-N(R^2)-C(O)O-$, $-O-C(O)-N(R^2)$, -C(O)-, -C(O)O-, -O-C(O)-, $-C(O)-N(R^2)-$, $-N(R^2)-C(O)-$, $-N(R^2)-$, $-C(R^2)_2-$, $-C(OR^2)_2-$;

each R is independently selected from hydrogen, $-R^2$, $-N(R^2)_2$, $-OR^2$, SR^2, $-C(O)-N(R^2)_2$, $-S(O_2)-N(R^2)_2$, or $-C(O)-OR^2$, wherein two adjacent R are optionally bound to one another and, together with each Y to which they are respectively bound, form a 4-8 membered carbocyclic or heterocyclic ring;

R^2 is selected from hydrogen, (C_1-C_3)-alkyl, or (C_1-C_3)-alkenyl; each optionally substituted with $-N(R')_2$, $-OR'$, SR', $-C(O)-N(R')_2$, $-S(O_2)-N(R')_2$, $-C(O)-OR'$, or R^3.

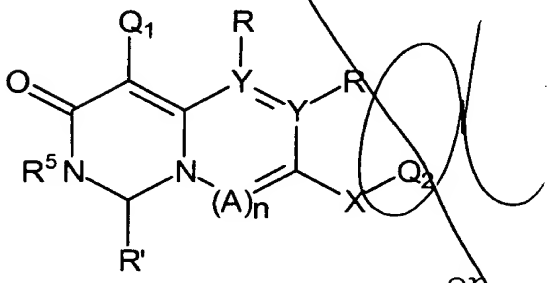
Y is selected from N or C;

A, if present, is selected from N or CR';

n is 0 or 1; and

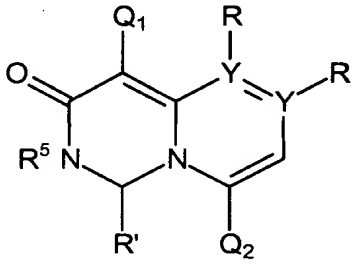
R_1 is selected from hydrogen, (C_1-C_3)-alkyl, OH, or $O-(C_1-C_3)$-alkyl.

2. A compound of the formula:



(Ic)

or

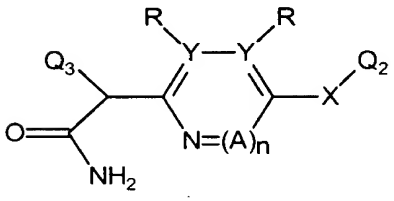


(Id)

wherein A, Q_1, Q_2, R, R', X, Y and n are defined in the same manner as set forth for compounds of formulae Ia and Ib; and

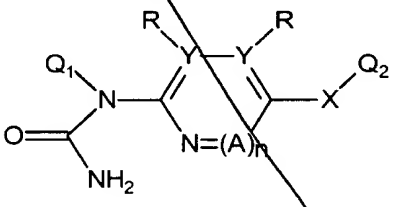
R^5 is selected from hydrogen, $-CR'_2OH$, $-C(O)R^4$, $-C(O)OR^4$, $-CR'_2OPO_3H_2$, and $-PO_3H_2$.

3. A compound of the formula:

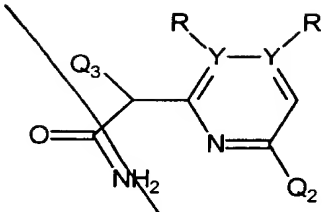


(Ie)

,

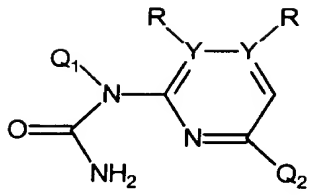


(If),



(Ig)

, or



(Ih)

wherein:

Q_3 is a 5-6 membered aromatic carbocyclic or heterocyclic ring system; or an 8-10 membered bicyclic ring system comprising aromatic carbocyclic rings, aromatic heterocyclic rings or a combination of an aromatic carbocyclic ring and an aromatic heterocyclic ring; wherein Q_3 is substituted with 1 to 4 substituents, each of which is independently selected from halo; C_1-C_3 alkyl optionally substituted with NR'_2, OR', CO_2R' or $CONR'_2$; O-(C_1-C_3)-alkyl optionally substituted with NR'_2, OR', CO_2R' or $CONR'_2$; NR'_2; OCF_3; CF_3; NO_2; CO_2R'; CONR'; SR'; $S(O_2)N(R')_2$; SCF_3; CN; $N(R')C(O)R^4$; $N(R')C(O)OR^4$; $N(R')C(O)C(O)R^4$; $N(R')S(O_2)R^4$; $N(R')R^4$; $N(R^4)_2$; OR^4; $OC(O)R^4$; $OP(O)_3H_2$; or N=C-$N(R')_2$; and

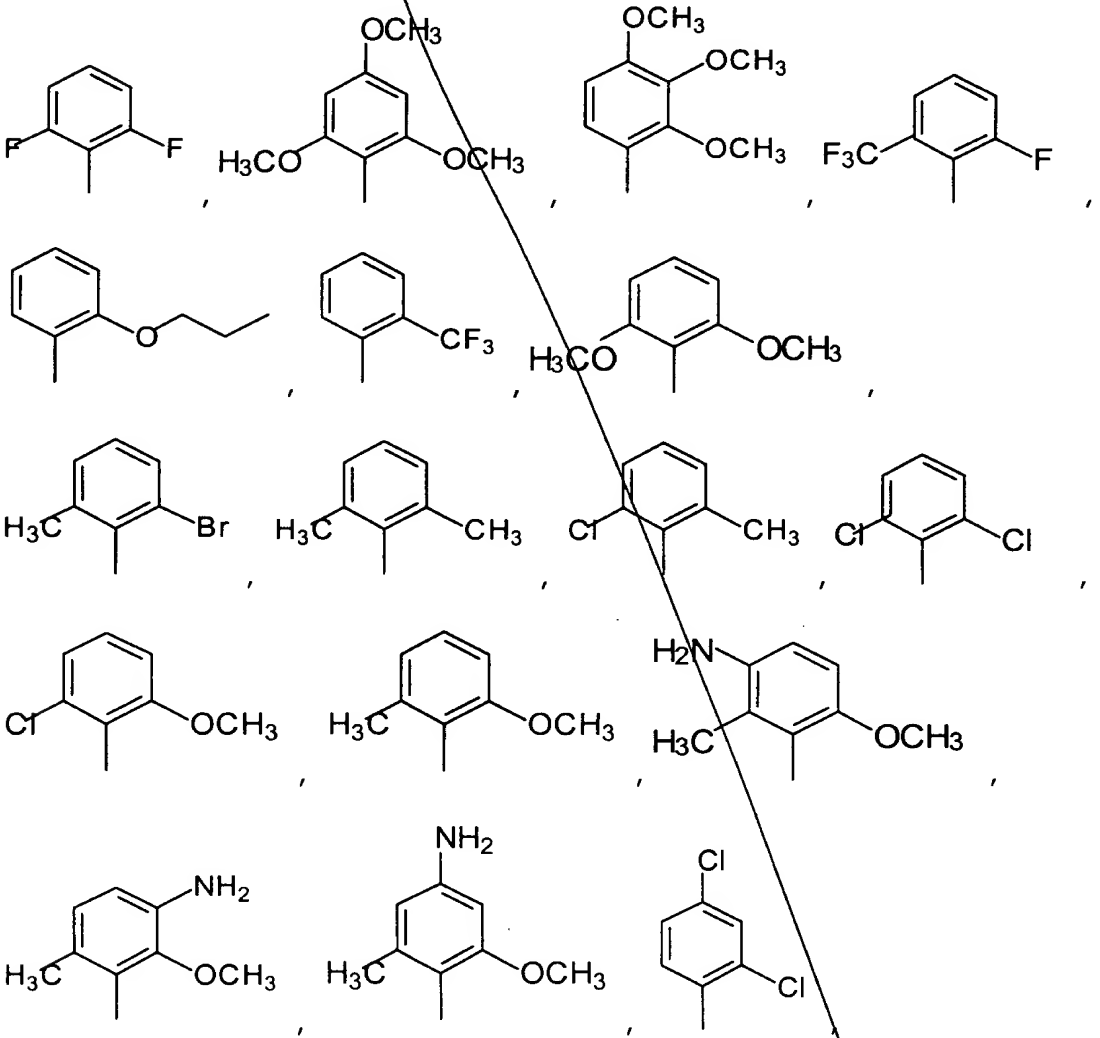
A, Q_1, Q_2, R, R', X, Y and n are defined as in claim 1.

4. The compound according to ~~any one of claims 1 to 3~~ claim 1, wherein Q_1 is selected from phenyl or pyridyl containing 1 to 3 substituents independently selected from chloro, fluoro, bromo, $-CH_3$, $-OCH_3$, -OH, $-CF_3$, $-OCF_3$, $-O(CH_2)_2CH_3$, NH_2, 3,4-methylenedioxy, $-N(CH_3)_2$, -NH-S(O)$_2$-phenyl, -NH-C(O)O-CH_2-4-pyridine, -NH-C(O)CH_2-morpholine,
-NH-C(O)CH_2-$N(CH_3)_2$, -NH-C(O)CH_2-piperazine,

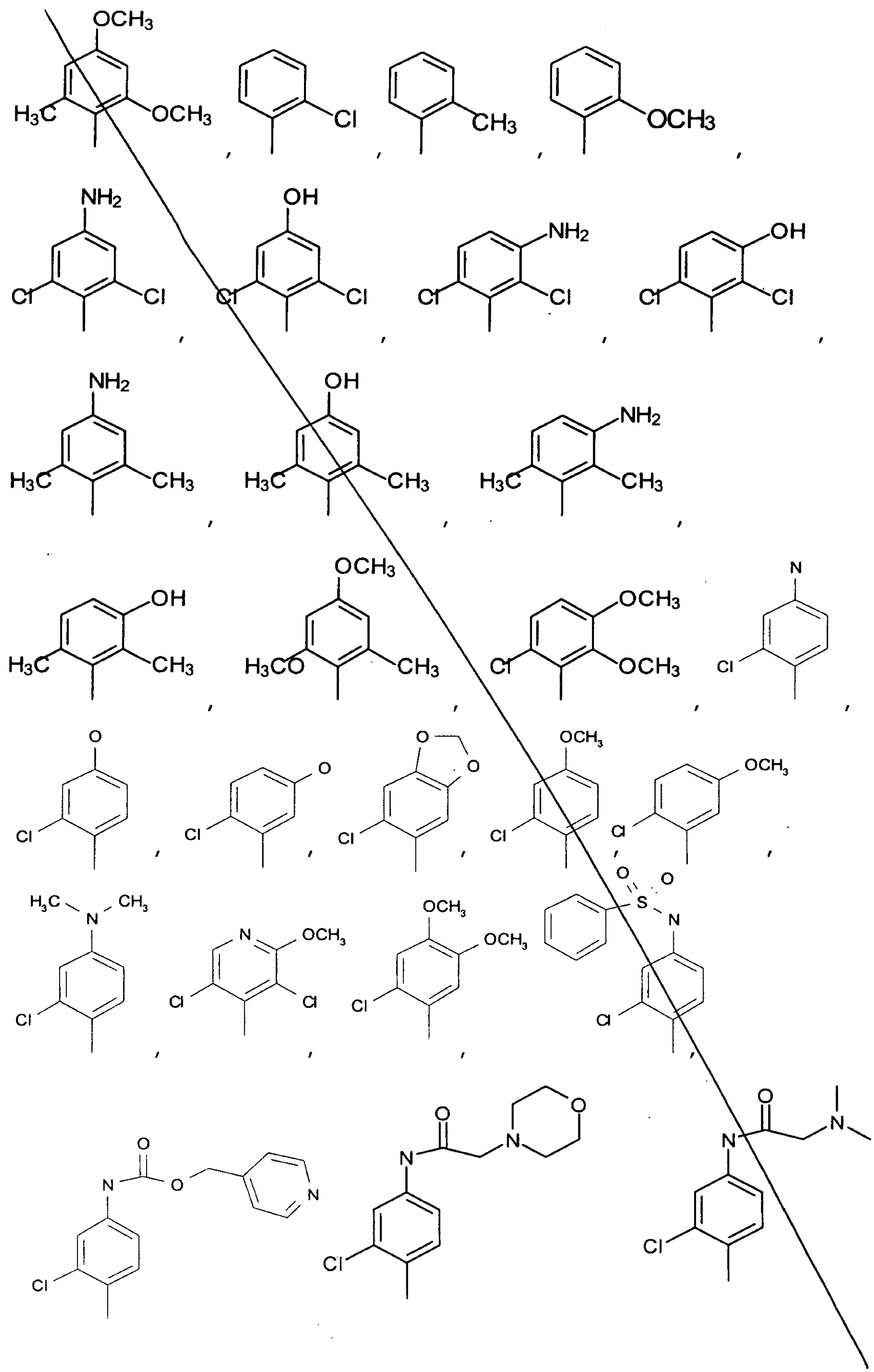
-NH-C(O)CH_2-pyrrolidine, -NH-C(O)C(O)-morpholine, -NH-C(O)C(O)-piperazine, -NH-C(O)C(O)-pyrrolidine, -O-C(O)CH_2-N$(CH_3)_2$, or -O-$(CH_2)_2$-N$(CH_3)_2$ and wherein at least one of said substituents is in the ortho position.

3 ~~5~~ The compound according to claim ~~4~~ 2 wherein Q_1 contains at least two substituents, both of which are in the ortho position.

6. The compound according to claim 4, wherein Q_1 is selected from:



B^2 Cont



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OCH3
NH2
OH
Cl
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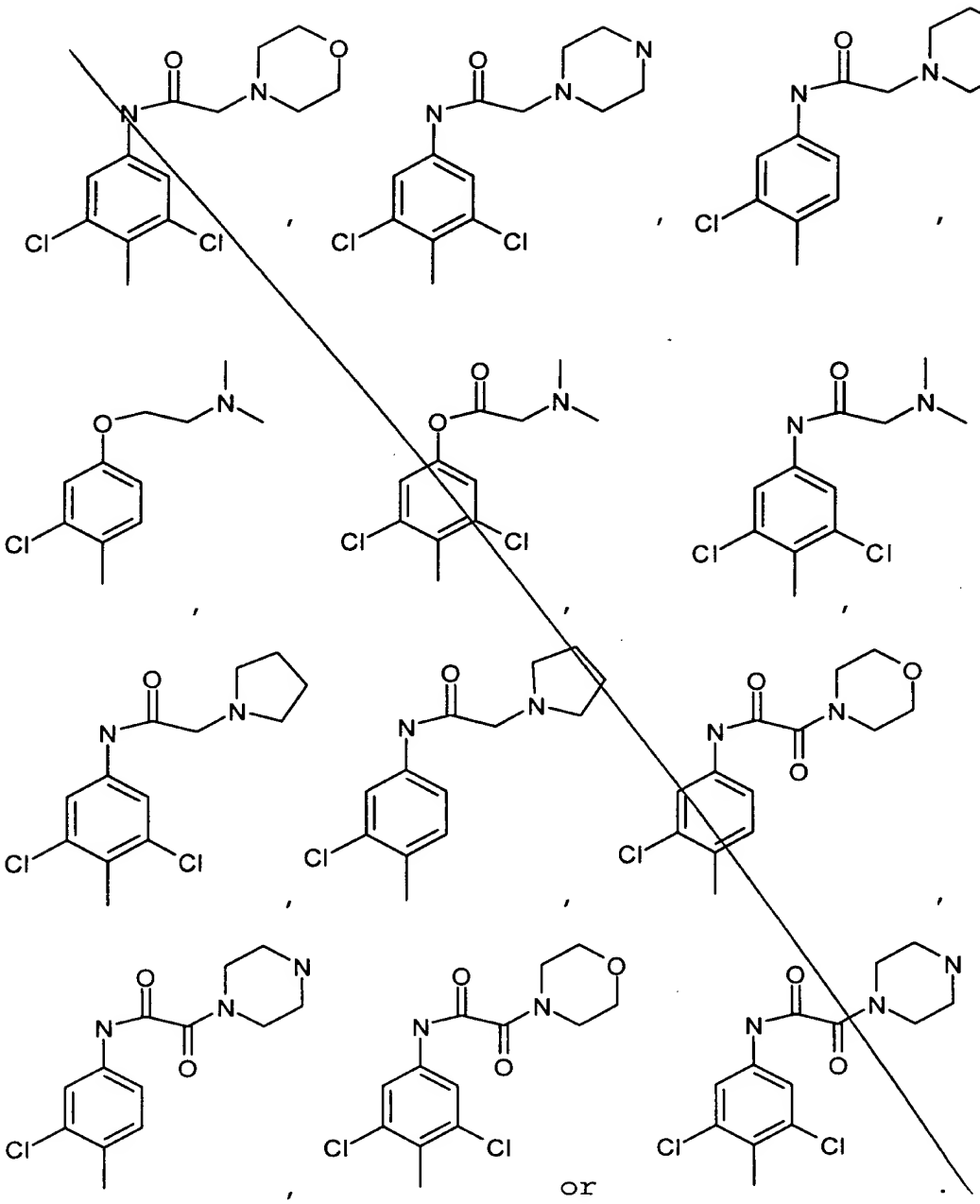
H3C
N
CH3
OCH3
O
S

B2 Cont



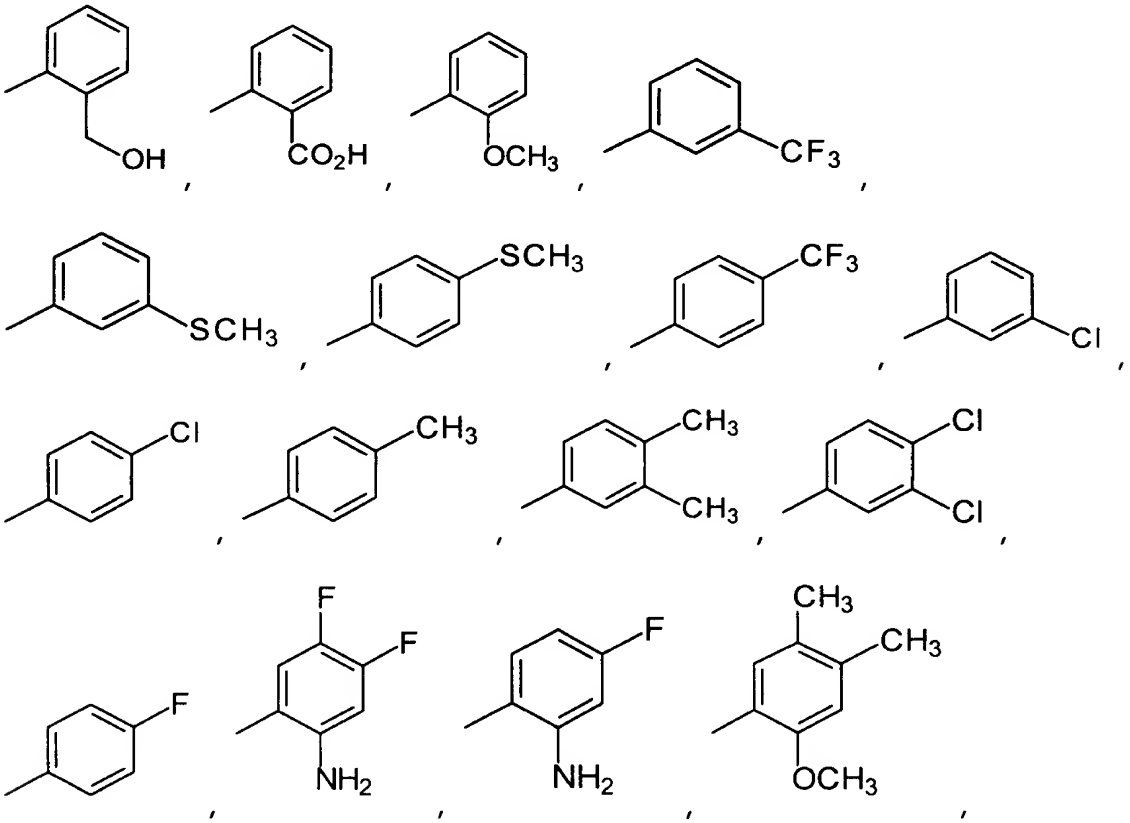
or

5 7 The compound according to claim 6 4 wherein Q_1 is selected from 2-fluoro-6-trifluoromethylphenyl, 2,6-difluorophenyl, 2,6-dichlorophenyl, 2-chloro-4-hydroxyphenyl, 2-chloro-4-aminophenyl, 2,6-dichloro-4-aminophenyl, 2,6-dichloro-3-aminophenyl, 2,6-dimethyl-4-

hydroxyphenyl, 2-methoxy-3,5-dichloro-4-pyridyl, 2-chloro-4,5 methylenedioxy phenyl, or 2-chloro-4-(N-2-morpholino-acetamido)phenyl.

~~8~~ 6 The compound according to ~~any one of claims 1 to 3,~~ claim 1 wherein Q_2 is selected from phenyl or pyridyl and wherein Q_2 optionally contains up to 3 substituents, each of which is independently selected from chloro, fluoro, bromo, methyl, ethyl, isopropyl, -OCH_3, -OH, -NH_2, -CF_3, -OCF_3, -SCH_3, -OCH_3, -C(O)OH, -$C(O)OCH_3$, -CH_2NH_2, -$N(CH_3)_2$, -CH_2-pyrrolidine and -CH_2OH.

~~9~~ 7 The compound according to claim ~~8~~ 6 wherein, Q_2 is selected from:



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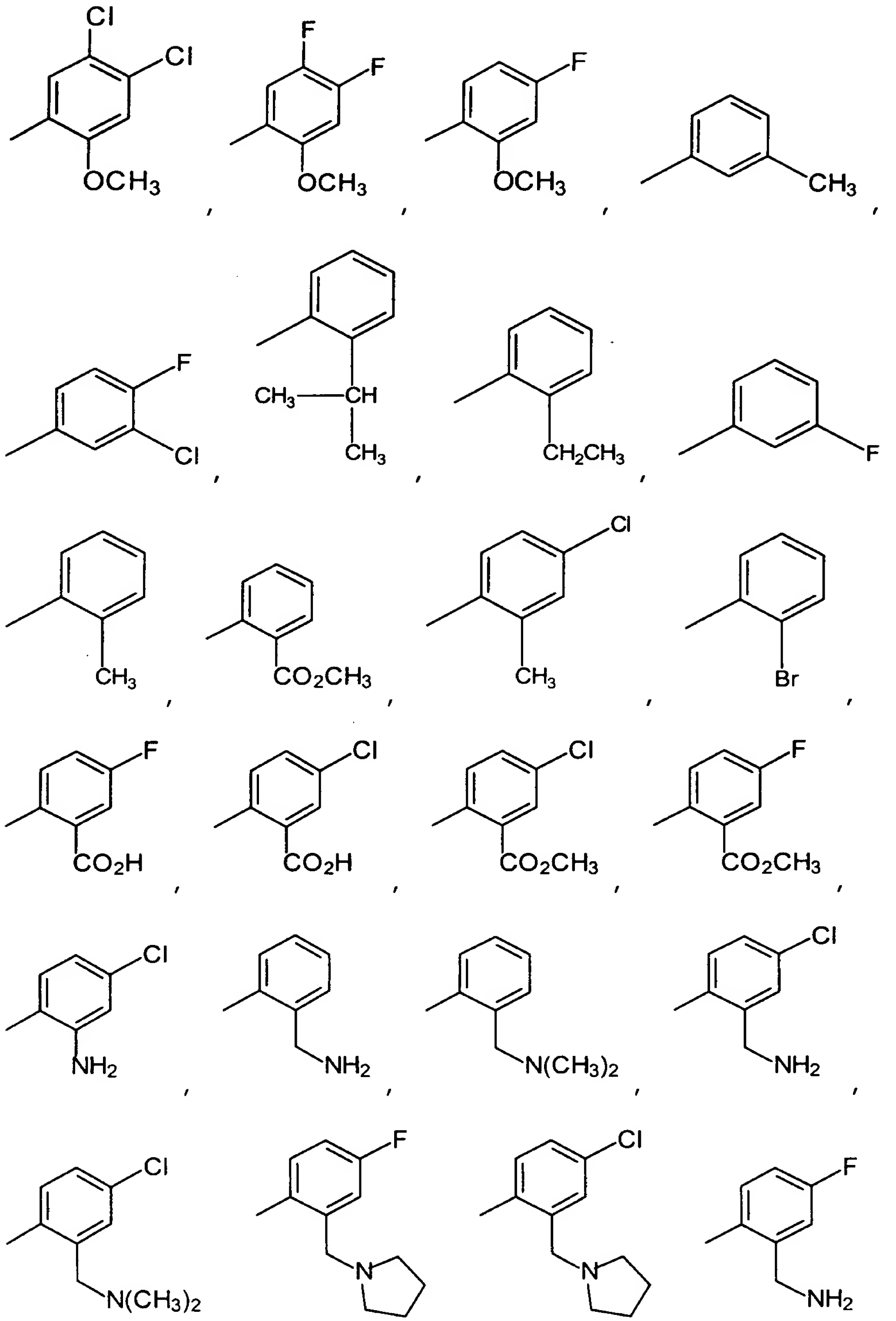
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CH3
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CO2CH3
Cl
CH3
Br
F
CO2H
Cl
CO2H
Cl
CO2CH3
F
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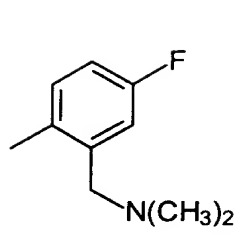
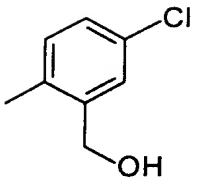
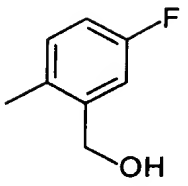
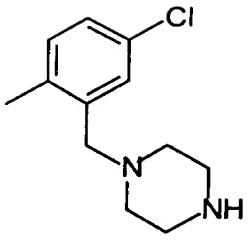
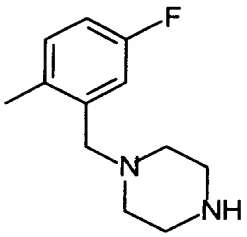
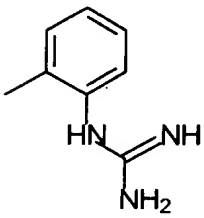
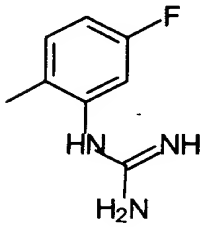
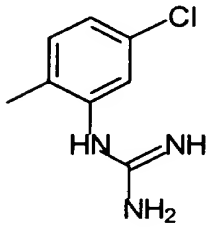
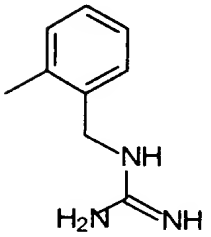
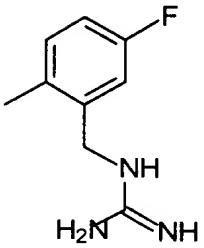
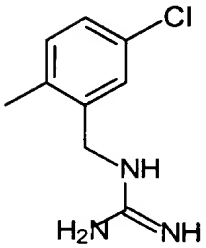
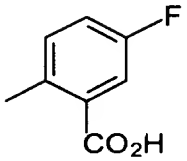
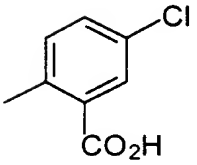
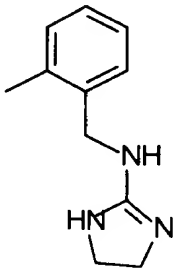
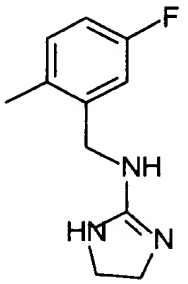
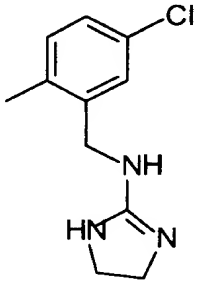
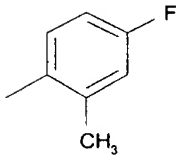
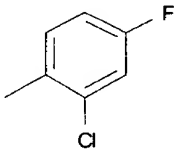
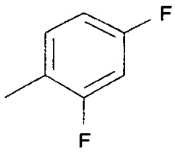
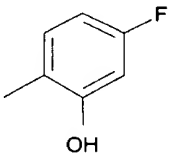
N
F
NH2

unsubstituted 2-pyridyl or unsubstituted phenyl.

10. The compound according to claim 9, wherein Q_2 is selected from phenyl, 2-isopropylphenyl, 3,4-dimethylphenyl, 2-ethylphenyl, 3-fluorophenyl, 2-methylphenyl, 3-chloro-4-fluorophenyl, 3-chlorophenyl, 2-carbomethoxylphenyl, 2-carboxyphenyl, 2-methyl-4-chlorophenyl, 2-bromophenyl, 2-pyridyl, 2-methylenehydroxyphenyl, 4-fluorophenyl, 2-methyl-4-fluorophenyl, 2-chloro-4-fluorphenyl, 2,4-difluorophenyl, 2-hydroxy-4-fluorphenyl or 2-methylenehydroxy-4-fluorophenyl.

11. The compound according to any one of claims 1 to 3, wherein X is selected from -S-, -O-, $-S(O_2)-$, -S(O)-, -NR-, $-C(R_2)-$ or -C(O)-.

12. The compound according to claim 10, wherein X is S.

13. The compound according to any one of claims 1 to 3, wherein n is 1 and A is N.

14. The compound according to any one of claims 1 to 3, wherein each Y is C.

15. The compound according to claim 14, wherein each R attached to Y is independently selected from hydrogen or methyl.

16. The compound according to claim 1, wherein said compound is selected from any one of compounds 2 to 3, or 5 to 53, depicted in Table 1.

17. The compound according to claim 2, wherein said compound is selected from any one of compounds 101 to 145 set forth in Table 2.

18. The compound according to claim 38, wherein Q_3 substituted with 2 to 4 substituents, wherein at least one of said substituents is present in the ortho position relative to the point of attachment of Q_3 to the rest of the inhibitor.

19. The compound according to claim 18, wherein both ortho positions are occupied by one of said independently selected substituents.

20. The compound according to claim 19, wherein Q_3 is a monocyclic carbocyclic ring; and each of said ortho substituents on Q_3 are independently selected from halo or methyl.

21. The compound according to claim 19, wherein Q_3 contains 1 to 2 substituents in addition to said ortho substituents, said additional substituents being independently selected from NR'_2, OR', CO_2R' CN, $N(R')C(O)R^4$; $N(R')C(O)OR^4$; $N(R')C(O)C(O)R^4$; $N(R')S(O_2)R^4$; $N(R')R^4$; $N(R^4)_2$; OR^4; $OC(O)R^4$; $OP(O)_3H_2$; or $N=C-N(R')_2$.

22. The compound according to claim 38, wherein said compound is a compound of formula Ie and is selected from any one of compounds 201 or 203 to 209, set forth in Table 3.

23. The compound according to claim 38, wherein said compound is a compound of formula Ig and is selected from any one of compounds 202/301, 302 to 399, or 1301, set forth in Table 4.

24. The compound according to claim 38, wherein said compound is a compound of formula Ih and is selected from any one of compounds 401 to 412, set forth in Table 5.

25 16 A pharmaceutical composition comprising an amount of a compound according to ~~any one of claims 1 to 3~~ claim 38 effective to inhibit p38, and a pharmaceutically acceptable carrier.

26. A method of treating or preventing inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, neurodegenerative diseases, allergies, reperfusion/ischemia in stroke, heart attacks, angiogenic disorders, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin-induced platelet aggregation or conditions associated with prostaglandin endoperoxidase synthase-2 in a patient, said method comprising administering to said patient a composition according to claim 25.

27. The method according to claim 26, wherein said method is used to treat or prevent an inflammatory disease selected from acute pancreatitis, chronic pancreatitis, asthma, allergies, or adult respiratory distress syndrome.

28. The method according to claim 26, wherein said method is used to treat or prevent an autoimmune disease selected from glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, or graft vs. host disease.

29. The method according to claim 26, wherein said method is used to treat or prevent a destructive bone disorders selected from osteoarthritis, osteoporosis or multiple myeloma-related bone disorder.

30. The method according to claim 26, wherein said method is used to treat or prevent a proliferative disease selected from acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, or multiple myeloma.

31. The method according to claim 26, wherein said method is used to treat or prevent an infectious disease selected from sepsis, septic shock, or Shigellosis.

32. The method according to claim 26, wherein said method is used to treat or prevent a viral disease

selected from acute hepatitis infection, HIV infection or CMV retinitis.

33. The method according to claim 26, wherein said method is used to treat or prevent a neurodegenerative disease selected from Alzheimer's disease, Parkinson's disease, cerebral ischemia or neurodegenerative disease caused by traumatic injury.

34. The method according to claim 26, wherein said method is used to treat or prevent ischemia/reperfusion in stroke or myocardial ischemia, renal ischemia, heart attacks, organ hypoxia or thrombin-induced platelet aggregation.

35. The method according to claim 26, wherein said method is used to treat or prevent a condition associated with prostaglandin endoperoxide synthase-2 selected from edema, fever, analgesia or pain.

36. The method according to claim 35, wherein said pain is selected from neuromuscular pain, headache, cancer pain, dental pain or arthritis pain.

37. The method according to claim 26, wherein said method is used to treat or prevent an angiogenic disorder selected from solid tumors, ocular neovasculization, or infantile haemangiomas.